

Tricyclic Heteroaromatic Ring Systems III¹. Synthesis of 1*H*,6*H*-Dipyrzolo[3,4—*b*:3',4'—*d*]pyridin-3-ones

Short Communication

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The reaction of hydrazines with substituted ethyl 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylates leads to the formation of 1*H*,6*H*-dipyrzolo[3,4—*b*:3',4'—*d*]pyridin-3-ones.

(Keywords: Pyrazolo[3,4—*b*]pyridines; Ring closures)

Tricyclische heteroaromatische Ringsysteme, III. Synthese von 1H,6H-Dipyrzolo[3,4—b:3',4'—d]pyridin-3-onen (Kurze Mitteilung)

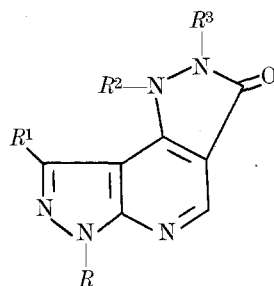
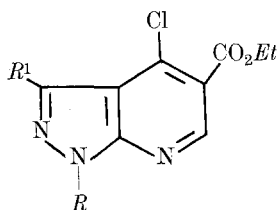
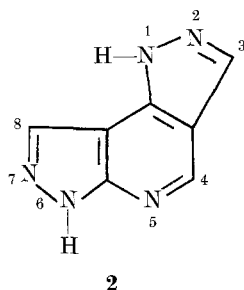
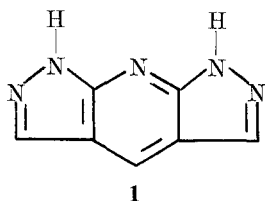
Die im Titel genannten Verbindungen wurden durch die Reaktion von Hydrazinen mit substituierten Ethyl-4-chlor-1*H*-pyrazolo[3,4—*b*]pyridin-3-carboxylaten dargestellt.

Introduction

Whereas the linear dipyrzolo[3,4—*b*:3',4'—*e*]pyridine ring system (**1**) has been known for some time³, the corresponding angular dipyrzolo[3,4—*b*:3',4'—*d*]pyridine ring system (**2**) has only recently been reported and some of its derivatives shown to act as tranquilizing and antiinflammatory agents⁴. During our studies on pyrazolo[3,4—*b*]pyridines⁵ we obtained a number of compounds which were transformed into derivatives of **2**.

Results and Discussion

The pyrazolo[3,4—*b*]pyridines (**3–6**) used in this work were obtained by “chloro-cyclization”⁶ of the corresponding ethyl α -carbethoxy- β -(pyrazol-5-ylamino)acrylates which in turn were obtained from the reaction of 5-aminopyrazoles with diethyl ethoxymethylenemalonate.



3 $R = R^1 = Me$

4 $R = Me, R^1 = Ph$

5 $R = R^1 = Ph$

6 $R = Ph, R^1 = Me$

7 $R = R^1 = Me, R^2 = R^3 = H$

8 $R = Me, R^1 = Ph, R^2 = R^3 = H$

9 $R = R^1 = Ph, R^2 = R^3 = H$

10 $R = Ph, R^1 = Me, R^2 = R^3 = H$

11 $R = R^1 = R^2 = Me, R^3 = H$

12 $R = R^2 = Me, R^1 = Ph, R^3 = H$

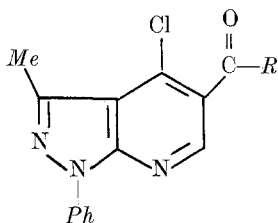
13 $R = R^1 = Ph, R^2 = Me, R^3 = H$

14 $R = Ph, R^1 = R^2 = Me, R^3 = H$

15 $R = Ph, R^1 = R^3 = H, R^2 = Me$

16 $R = R^3 = Ph, R^1 = Me, R^2 = H$

17 $R = R^2 = Ph, R^1 = Me, R^3 = H$



18 $R = OH$

19 $R = Cl$

The reaction of **3-6** with hydrazine and methylhydrazine leads to the desired tricyclic compounds **7-15**. From the reaction of **6** with phenylhydrazine an open chain derivative was formed which on treatment with acetic acid ringclosed to **16** with the phenyl ring on N-2. The isomeric compound **17** having the phenyl ring on N-1 was obtained indirectly. The chloroester (**6**) was hydrolyzed to the corresponding acid

(18) and then transformed into its acid chloride (19) which on reaction with phenylhydrazine at room temperature followed by heating in dioxan gave the isomeric tricyclic compound 17. The data of these dipyrazolopyridines are presented in Table 1.

The signals for the protons of N-methyl groups (at N-1 or N-6) are between δ 4.00 and 4.15 ppm and for the protons of the C-methyl group (at C-8) between 2.63 and 2.75 for the majority of the compounds. However, in 12 and 13 the N-methyl proton signals were observed at 3.32 and in 17 the C-methyl proton-signal at 1.75. These upfield shifts for the methyl protons are ascribed to the ring-current-shielding of the benzene ring on C-8 and N-1, respectively. These anisotropic shielding effects of phenyl groups have earlier been noticed in other tricyclic systems⁷.

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Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 Mc/s (tetramethylsilane as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer and were measured in potassium bromide disks. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240.

Ethyl 4-chloro-1,3-dimethylpyrazolo[3,4-*b*]pyridine-5-carboxylate (3) mp 93-94°; ethyl 4-chloro-1-methyl-3-phenylpyrazolo[3,4-*b*]pyridine-5-carboxylate (4) mp 130-131°; ethyl 4-chloro-1,3-diphenyl-pyrazolo[3,4-*b*]pyridine-5-carboxylate (5) mp 162-163°; and ethyl 4-chloro-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine-5-carboxylate (6) mp 110° used in this work were all obtained by the chlorocyclization of the corresponding ethyl α -carbethoxy- β -(pyrazol-5-ylamino)acrylates⁵.

*1H,6H-Dipyrazolo[3,4-*b*:3',4'-*d*]pyridin-3-one*

General Method. An equimolar mixture of a chloroester (3-6) and hydrazine hydrate or methylhydrazine in 5-10 ml of ethanol was heated under reflux for 15 h (hydrazine hydrate) or 3 h (methylhydrazine). The reaction mixture was concentrated, diluted with water, filtered and washed with water. The cyclized product thus obtained was dried and crystallized from an appropriate solvent to give 7-15 (Table 1).

*2,6-Diphenyl-8-methyldipyrazolo[3,4-*b*:3',4'-*d*]pyridin-3-one* (16)

A mixture of 0.9 g of 6, 0.3 g of phenylhydrazine in 10 ml of ethanol was heated under reflux to give 0.88 g (80%) of *N*-phenyl-*N'*-(5-carbethoxy-3-methyl-1-phenylpyrazolo[3,4-*b*]pyrid-4-yl)hydrazine as light brown crystals

Table 1. *1H,6H-Dipyrrozolo[3,4-b:3',4'-d]pyridin-3-ones*

Compd. No.	Yield (%)	mp° (from)	Molecular formula ^a	IR (cm ⁻¹)	PMR (<i>J</i> in Hz) ^b (temp°)
7	84	258-259 (AcOH)	C ₉ H ₉ N ₅ O	3 250-2 400 (NH); 1 640 (C=O)	2.63 (3H, s, C-Me); 4.04 (3H, s, N-Me); 8.89 (1H, s, H-4); 9.10 (br., NH). (60)
8	89	278-279 (AcOH)	C ₁₄ H ₁₁ N ₅ O	3 300-2 500 (NH) 1 645 (C=O)	4.15 (3H, s, N-Me); 7.40-8.20 (5H, m, <i>Ph</i>); 8.81 (1H, s, H-4); 10.00 (br., NH). (80)
9	85	288-289 (AcOH)	C ₁₉ H ₁₃ N ₅ O	3 380-2 500 (NH) 1 640 (C=O)	3.35 (br., NH); 7.40-8.40 (10H, m, <i>Ph</i>); 8.90 (1H, s, H-4). (34)
10	86	278-279 (AcOH)	C ₁₄ H ₁₁ N ₅ O	3 300-2 800 (NH) 1 648 (C=O)	2.75 (3H, s, C-Me); 7.30-8.40 (5H, m, <i>Ph</i>); 8.87 (1H, s, H-4); 12.00 (br., NH). (34)
11	96	295-297 (EtOH)	C ₁₀ H ₁₁ N ₅ O	3 250-2 350 (NH) 1 630 (C=O)	2.70 (3H, s, C-Me); 4.00 (3H, s, N-Me); 4.03 (3H, s, N-Me); 8.75 (1H, s, H-4). (100)
12	95	> 300 (AcOH)	C ₁₅ H ₁₃ N ₅ O	3 200-2 300 (NH) 1 625 (C=O)	3.32 (s, N-1-Me + NH + H ₂ O); 4.15 (3H, s, N-6-Me); 7.58 (5H, s, <i>Ph</i>); 8.75 (1H, s, H-4). (34)
13	95	> 300 (AcOH)	C ₂₀ H ₁₅ N ₅ O	3 250-2 400 (NH) 1 630 (C=O)	3.32 (3H, s, N-Me); 7.30-8.50 (10H, m, <i>Ph</i>); 8.84 (1H, s, H-4). (100)
14	77	> 300 (EtOH)	C ₁₅ H ₁₃ N ₅ O	3 300-2 100 (NH) 1 630 (C=O)	2.75 (3H, s, C-Me); 4.15 (3H, s, N-Me); 7.30-8.50 (5H, m, <i>Ph</i>); 8.68 (1H, s, H-4); 11.25 (br., NH). (34)
15	17	> 300 (EtOH)	C ₁₄ H ₁₁ N ₅ O	3 250-2 100 (NH) 1 645 (C=O)	3.30 (br., NH); 4.15 (3H, s, N-Me); 7.30-8.50 (5H, m, <i>Ph</i>); 8.64 (1H, s, H-8); 8.79 (1H, s, H-4). (50)
16	98	> 300 (AcOH)	C ₂₀ H ₁₅ N ₅ O	3 200-2 500 (NH) 1 640 (C=O)	2.69 (3H, s, C-Me); 7.20-8.20 (10H, m, <i>Ph</i>); 8.61 (1H, s, H-4). (50)
17	86	> 300 (AcOH)	C ₂₀ H ₁₅ N ₅ O	3 200-2 300 (NH) 1 625 (C=O)	1.75 (3H, s, C-Me); 7.50 (5H, s, <i>Ph</i> -1); 7.30-8.30 (5H, m, <i>Ph</i> -6); 8.89 (1H, s, H-4); 11.00-12.00 (br., NH). (80)

^a Elemental analyses are in full agreement with the calculated values.^b Solvent *DMSO-d*₆.

mp 180–181° (ethanol). PMR (CDCl_3) δ : 1.35 (3H, t, $J = 7\text{ Hz}$, $\text{CH}_3\text{—CH}_2\text{—OCO}$); 3.48 (3H, s, *Me*-3); 4.30 (2H, q, $J = 7\text{ Hz}$, $\text{CH}_3\text{—CH}_2\text{—OCO}$); 6.30 (1H, s, *Ph*— NH—N); 6.68–7.30 and 8.00–8.30 (10H, m, arom.); 8.89 (1H, s, H-6); 10.48 (1H, s, *Ph*— NH—NH). IR cm^{-1} : 3260 and 3250–2800 (NH); 1680 (CO, ester).

On heating the hydrazine obtained above in 10 ml of acetic acid for 4 h. **16** was isolated from the reaction mixture on diluting with water and crystallization (Table 1).

1,6-Diphenyl-8-methyl-1H,6H-dipyrazolo[3,4—b:3',4'—d]pyridin-3-one (17)

A solution of 20 ml of acetic acid and hydrochloric acid and 0.95 g of (**16**) was heated under reflux for a period of 3 h and the product filtered off to give 0.81 g (94%) of 4-chloro-3-methyl-1-phenylpyrazolo[3,4—b]pyridine-5-carboxylic acid (**18**) as colorless crystals, mp 236–237° (*AcOH*). PMR ($\text{DMSO}-d_6$) δ : 2.64 (3H, s, *Me*); 7.40–8.10 (5H, m, arom.); 8.58 (1H, s, H-6). IR cm^{-1} : 3300–2900 (OH); 1725 (CO, acid); 1600, 1498, 1190, 755, 690.

The acid **18** was converted into its acid chloride **19** by heating under reflux 0.5 g of **18** with 5 ml of thionyl chloride for 1 h and the excess thionyl chloride evaporated under reduced pressure. To the cooled residue 10 ml of dioxan and 0.2 g of phenylhydrazine was added and left at room temperature with stirring for 0.5 h and then heated under reflux for 4 h, diluted with water, filtered and purified to give **17** (Table 1).

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